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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/666,870	09/20/2000	Andrew D. Ellington	119927-1030	8382
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30623 7590 01/29/2003

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EXAMINER

EPPERSON, JON D

ART UNIT

PAPER NUMBER

1639

DATE MAILED: 01/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary*File Copy*

Application No.

09/666,870

Applicant(s)

ELLINGTON ET AL.

Examiner

Jon D Epperson

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1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on December 2, 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-53 is/are pending in the application.
- 4a) Of the above claim(s) 1-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 47-53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14. 6) ☐ Other:

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DETAILED ACTION

Please note: The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

Status of the Application

1. Receipt is acknowledged of a Response to a Restriction Requirement, which was dated on December 2, 2002 (Paper No. 17).

Priority Claims

2. The priority filing date of June 15, 2000 for application 60/212,097 is acknowledged.

Status of the Claims

3. Claims 1-53 are pending in the present application.
4. Applicant's response to the Restriction and/or Election of Species requirements in Paper No. 17 is acknowledged (i.e., applicant elected Group IV, claims 47-53, without traverse) and claims 1-46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim.
5. Therefore, claims 47-53 are examined on the merits in this action.

Information Disclosure Statement

6. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

7. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

8. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)).

9. The use of the trademarks (e.g., CenturyTM Marker ladder on page 45, line 18, please note that numerous trademarks are used through the specification) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

10. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Objections to the Claims

11. Claim(s) 51-53 are objected to because of the following informalities:

A. Claims 51-53 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 50. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 50-53 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination

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of Patent Applications Under the 35 USC 112, ¶ 1 “Written Description” Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claims 50-53 outlines steps for detecting an aptazyme reaction wherein the aptazyme construct comprises any “modified nucleotides” to inhibit degradation of the aptazyme. The scope of this claim includes an infinite number of structural variants (i.e., modifications) wherein no distinguishing structural attributes are provided for the members of said modified nucleotides. The specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the modified nucleotides. Furthermore, the specification does not disclose any specific examples of “modified nucleotides.” Consequently, the specification and claims do not provide any guidance as to what structural features all of these modified nucleotides might share. Therefore, it is not possible to determine *a priori* which compounds the genus of modified nucleotides would encompass because there is no common structural attributes that can link together all of these nucleotides i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* all the different types of compounds that should be included in this genus from the lack of examples provided by applicants.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify all of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, applicants have not provided enough examples (indeed they have not provided any examples) to

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teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus.

Thus, applicant was not in possession of the claimed genus.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 47-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 47**, the term phrase “providing a substrate comprising a solid support and an aptazyme construct or a heterogeneous mixture of aptazyme constructs covalently immobilized on the support” is vague and indefinite. For example, it is not clear if applicant contends the substrate to comprise (1) a solid support and an aptazyme construct (i.e., wherein the aptazyme construct does not have to be “covalently attached” to the solid support) “OR” (2) a heterogeneous mixture of aptazyme construct covalently immobilized on the solid support (i.e., wherein the aptazyme construct has to be “covalently attached to the solid support)? Or does applicant contend the substrate to comprise (3) a solid support and an aptazyme construct or a heterogenous mixture of aptazyme constructs that are covalently immobilized on the support (i.e., wherein the “aptazyme” or “heterogeneous mixture of aptazyme” are covalently attached to the solid

support in either case). The sentence structure is confusing. Applicants are requested to clarify and/or correct. Therefore, claims 47 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. **Claim 47** recites the limitation "the support" in lines 5-6. There is insufficient antecedent basis for this limitation in the claim. The Examiner recommends "the solid support." Therefore, claim 47 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. **Claims 50-53** recite the limitation "the aptazyme" in line 3. There is insufficient antecedent basis for this limitation in the claim. The Examiner recommends "the immobilized aptazyme." Therefore, claim 47 and all dependent claims are rejected under 35 USC 112, second paragraph.

D. For **claims 50-53**, the phrase "modified nucleotides to inhibit degradation of the aptazyme" is vague and indefinite. For example, it is not clear what structural "modifications" would be required to inhibit degradation of the aptazyme? Consequently, the metes and bounds of claims 50-53 cannot be determined. Therefore, claims 50-53 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. Claims 47 and 49 are rejected under 35 U.S.C. 102(a) as being anticipated by Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" *Nature Structural Biology* **November 1999**, 6 (11), 992-4).

For *claim 47*, Marshall et al discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins (see Marshall et al, entire document, especially figure 3; see also page 994, last paragraph), which anticipates claim 47. For example, Marshall et al discloses aptazyme chips for "monitor[ing] the presence and concentrations of different metabolites or proteins" wherein a "ribozyme ligase", which anticipates the preamble of claim 47 because an "aptazyme reaction" is being "detected" when the ribozyme ligase covalently bonds to a reporter in the presence of cognate effectors. Marshall et al also discloses "aptazymes" on a solid support, which reads on lines 2-5 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... are shown immobilized on beads in wells ... [o]ne advantage of this scheme is that covalent immobilization of reporters ... should allow extremely stringent wash steps to be employed"). Marshall et al also discloses "at least one analyte" and "providing substrate tagged to be detectable" in lines 7-8 of claim 47 (see Marshall et al, figure 3, "ribozyme ligases ... immobilized on beads in wells and mixtures of analytes and fluorescently tagged substrates have been added to each well"). Marshall et al also discloses the immobilization of a substrate to the aptazyme upon activation of the aptazyme with an

analyte wherein a signal is produced after washing unbound substrate off the substrate (see Marshall et al, figure 3, “after reaction and washing, the presence and amounts of co-immobilized fluorescent tags are indicative of the amounts of ligands that were present during the reaction”). Please also note that Marshall et al discloses applicants preferred embodiment (compare Marshall et al, figure 3 and page 994, last paragraph to applicant’s specification, pages 60-61, especially page 60, line 19 which references the Marshall et al paper).

For **claim 49**, Marshall et al discloses the use of “amplification” for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (see Marshall et al, figure 1) (see also Marshall, page 994 last paragraph, “Interestingly, aptazyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection”), which anticipates claim 49.

15. Claims 47 and 49 are rejected under 35 U.S.C. 102(a) as being anticipated by Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. “In vitro selection of nucleic acids for diagnostic applications” Reviews in Molecular Biotechnology March 2000, 74, 15-25).

For **claim 47**, Hesselberth et al discloses methods for the “high-throughput construction of chips to sense proteomes and metabolomes” (see Hesselberth et al, entire document, pages 23-24; section 5), which anticipates claim 47. For example, Hesselberth et al discloses that “aptazymes” can be “covalently immobilize[d] ... in discrete sectors of

arrays” like “chip[s]” (see Hesselberth et al, page 24, last paragraph, “For example, a host of signaling aptamers could be synthesized with terminal amines, immobilized on glass, and an analyte mixture could be applied to the glass surface”). Hesselberth et al also discloses method steps for using the immobilized aptazymes to detect individual analytes by their ability to “pull down” labeled substrates that can then be detected after washing away unbound substrate (see Hesselberth et al, page 24, last paragraph, “The presence of quantities of individual analytes could then be determined by monitoring the changes in fluorescence intensity in individual sectors of the chip. Similarly, aptazymes could be immobilized and analytes and oligonucleotide tags introduced together. Since the pairing between the aptazymes and the oligonucleotide tags can be altered at will, analytes could activate specific aptamers in specific sectors to pull down specific tags. In this way, analyte detection might not only be spatially but also spectrally resolved. Moreover because the tags are covalently immobilized to the aptazyme, which in turn covalently immobilized to the chip surface, aptazyme chips can be stringently washed to reduce non-specific binding and background”).

For **claim 49**, Hesselberth et al discloses the ribozymes with appended tags can be “preferentially amplified” (see Hesselberth et al, entire document, especially page 16, paragraph 1), which anticipates claim 49.

Claims Rejections – 35 U.S.C. 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 47-49 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" *Nature Structural Biology* **November 1999**, 6 (11), 992-4).

For *claim 47*, Marshall et al discloses "aptazyme chips" wherein different ribozyme ligases are immobilized on beads in wells to monitor the presence and concentrations of different metabolites or proteins (see Marshall et al, entire document,

especially figure 3; see also page 994, last paragraph), which anticipates claim 47. For example, Marshall et al discloses aptazyme chips for “monitor[ing] the presence and concentrations of different metabolites or proteins” wherein a “ribozyme ligase”, which anticipates the preamble of claim 47 because an “aptazyme reaction” is being “detected” when the ribozyme ligase covalently bonds to a reporter in the presence of cognate effectors. Marshall et al also discloses “aptazymes” on a solid support i.e., they are disclosing “apatazyme chips”, which reads on lines 2-5 of claim 47 (see Marshall et al, figure 3, “ribozyme ligases ... are shown immobilized on beads in wells ... [o]ne advantage of this scheme is that covalent immobilization of reporters ... should allow extremely stringent wash steps to be employed”). Marshall et al also discloses “at least one analyte” and “providing substrate tagged to be detectable” in lines 7-8 of claim 47 (see Marshall et al, figure 3, “ribozyme ligases ... immobilized on beads in wells and mixtures of analytes and fluorescently tagged substrates have been added to each well”). Marshall et al also discloses the immobilization of a substrate to the aptazyme upon activation of the aptazyme with an analyte wherein a signal is produced after washing unbound substrate off the substrate (see Marshall et al, figure 3, “after reaction and washing, the presence and amounts of co-immobilized fluorescent tags are indicative of the amounts of ligands that were present during the reaction”).

For **claim 48**, although Marshall et al does not specifically mention the use of “automation” with disclosed methods for using “aptazyme chips”, automation would be obvious to one of ordinary skill in the art because “chip” are made for automation i.e.,

they are used and designed for high throughput screening. See *In re Schaumann*, 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

For **claim 49**, Marshall et al discloses the use of “amplification” for increasing the amount of aptamer or aptazyme with the desired characteristics and thus increase the signal produced (see Marshall et al, figure 1) (see also Marshall, page 994 last paragraph, “Interestingly, aptazyme ligases have the unique property of being able to transduce effectors into templates that can be amplified, affording an additional boost in signal prior to detection”), which anticipates claim 49.

18. Claims 47-49 are rejected under 35 U.S.C. 102(a) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. “In vitro selection of nucleic acids for diagnostic applications” *Reviews in Molecular Biotechnology* March 2000, 74, 15-25).

For **claim 47**, Hesselberth et al discloses methods for the “high-throughput construction of chips to sense proteomes and metabolomes” (see Hesselberth et al, entire document, pages 23-24; section 5), which anticipates claim 47. For example, Hesselberth et al discloses that “aptazymes” can be “covalently immobilize[d] ... in discrete sectors of arrays” like “chip[s]” (see Hesselberth et al, page 24, last paragraph, “For example, a host of signaling aptamers could be synthesized with terminal amines, immobilized on glass, and an analyte mixture could be applied to the glass surface”). Hesselberth et al also discloses method steps for using the immobilized aptazymes to detect individual analytes

by their ability to “pull down” labeled substrates that can then be detected after washing away unbound substrate (see Hesselberth et al, page 24, last paragraph, “The presence of quantities of individual analytes could then be determined by monitoring the changes in fluorescence intensity in individual sectors of the chip. Similarly, aptazymes could be immobilized and analytes and oligonucleotide tags introduced together. Since the pairing between the aptazymes and the oligonucleotide tags can be altered at will, analytes could activate specific aptamers in specific sectors to pull down specific tags. In this way, analyte detection might not only be spatially but also spectrally resolved. Moreover because the tags are covalently immobilized to the aptazyme, which in turn covalently immobilized to the chip surface, aptazyme chips can be stringently washed to reduce non-specific binding and background”).

For **claim 48**, although Hesselberth et al does not specifically mention the use of “automation” with disclosed methods for using the “chips”, automation would be would be immediately envisaged (e.g., anticipated) or in the alternative prima facie obvious to one of ordinary skill in the art because “chip” are made for automation i.e., they are used and designed for high throughput screening. See *In re Schaumann*, 572 F.2d 312. 197 USPQ 5 (CCPA 1978).

For **claim 49**, Hesselberth et al discloses the ribozymes with appended tags can be “preferentially amplified” (see Hesselberth et al, entire document, especially page 16, paragraph 1), which anticipates claim 49.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

20. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" *Nature Structural Biology* **November 1999**, 6 (11), 992-4) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" *Biotechnol. Prog.* **1998**, 14, 845-850).

For **claims 47 and 49**, Marshall et al teaches all the limitations stated in the 35 U.S.C. 102(a) rejection above (incorporated in its entirety herein by reference), which anticipates claims 47 and 49 and, consequently, also renders obvious claims 47 and 49.

For **claim 48**, the prior art teachings of Marshall et al differs from the claimed invention by not specifically reciting the use of a “automation” for the method of detecting an aptazyme reaction. Marshall et al is deficient in that it only teaches the use of “chips”, which only implies that automation would be used since chips are designed for large scale automation (see Marshall et al, page 993, figure 3).

However, Cox teaches that in vitro selection can be “automated” (see entire document, especially figure 1).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method of Marshall et al with the “automation” equipment as taught by Cox et al because Cox et al teaches that their automation procedures can be used with aptamers in procedures that involve in vitro selection as required by the method steps Marshall et al. Furthermore, one of ordinary skill in the art would have been motivated to use a “automation” because Cox explicitly states that “[a]utomated selection can now be used to generate nucleic acid aptamers in days rather than weeks or months” i.e. one of skill in the art would have immediately recognized the time savings that could be obtained through automation and the possibility of increased throughput (see Cox et al, entire document, especially abstract).

22. Claims 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. “In vitro selection of nucleic acids for diagnostic applications” Reviews in Molecular Biotechnology March 2000, 74, 15-25)

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and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" Biotechnol. Prog. 1998, 14, 845-850).

For **claims 47 and 49**, Hesselberth et al teaches all the limitations stated in the 35 U.S.C. 102(a) rejection above (incorporated in its entirety herein by reference), which anticipates claims 47 and 49 and, consequently, also renders obvious claims 47 and 49.

For **claim 48**, the prior art teachings of Hesselberth et al differs from the claimed invention by not specifically reciting the use of a "automation" for the method of detecting an aptazyme reaction. Hesselberth et al is deficient in that it only teaches the use of "chips", which only implies that automation would be used since chips are designed for large scale automation (see Hesselberth et al, page 24, last paragraph; see also abstract).

However, Cox teaches that in vitro selection can be "automated" (see entire document, especially figure 1).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method of Hesselberth et al with the "automation" equipment as taught by Cox et al because Cox et al teaches that their automation procedures can be used with aptamers in procedures that involve *in vitro* selection as required by the method steps Hesselberth et al. Furthermore, one of ordinary skill in the art would have been motivated to use a "automation" because Cox explicitly states that "[a]utomated selection can now be used to generate nucleic acid aptamers in days rather than weeks or months" i.e. one of skill in the art would have immediately recognized the time savings that could

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be obtained through automation and the possibility of increased throughput (see Cox et al, entire document, especially abstract).

23. Claims 47-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marshall et al (Marshall, K. A.; Ellington, A. D. "Training ribozymes to switch" *Nature Structural Biology* **November 1999**, 6 (11), 992-4) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" *Biotechnol. Prog.* **1998**, 14, 845-850) and Scaringe et al (Scaringe, S. A.; Wincott, F. E.; Caruthers, M. H. "Novel RNA Synthesis Method Using 5'-O-silyl-2'-O-orthoester Protecting Groups" *J. Am. Chem. Soc.* **1998**, 120, 11820-11821).

For **claims 47-49**, the combined teaches of Marshall et al and Cox et al teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 47-49.

For **claims 50-53**, the prior art teachings of Marshall et al combined with Cox et al differ from the claimed invention by not specifically reciting the use of a "modified nucleotides to inhibit degradation of the aptazyme."

However, Scaringe et al teaches the use of 5'-O-silyl-2'-O-orthoester protecting groups that will "minimize" the opportunity to degrade the RNA (see entire document, especially page 11821, last paragraph).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method automated in vitro selection methods of Marshall et al and Cox et al with the "modified" nucleotides of Scaringe et al because Scaringe et al states that these protective groups can be used with RNA and will prevent degradation of said

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RNA and thus would be obvious to use in situations where the degradation of RNA is to be avoided. Furthermore, one of ordinary skill in the art would have been motivated to use the protecting groups of Scaringe et al because Scaringe et al states that these protecting groups would be useful for solid-phase synthesis and purification of said RNA that subsequently is utilized in the screening methods because RNA has to be "provided" (see Scaringe et al, entire document; see especially page 11821, last paragraph).

24. Claims 47-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hesselberth et al (Hesselberth, J.; Robertson, M. P.; Jhaveri, S.; Ellington, A. D. "In vitro selection of nucleic acids for diagnostic applications" *Reviews in Molecular Biotechnology* March 2000, 74, 15-25) and Cox et al (Cox, J. C.; Rudolph, P.; Ellington, A. D. "Automated RNA Selection" *Biotechnol. Prog.* **1998**, 14, 845-850) and Scaringe et al (Scaringe, S. A.; Wincott, F. E.; Caruthers, M. H. "Novel RNA Synthesis Method Using 5'-O-silyl-2'-O-orthoester Protecting Groups" *J. Am. Chem. Soc.* **1998**, 120, 11820-11821).

For **claims 47-49**, the combined teachings of Hesselberth et al and Cox et al teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 47-49.

For **claims 50-53**, the prior art teachings of Hesselberth et al combined with Cox et al differ from the claimed invention by not specifically reciting the use of a "modified nucleotides to inhibit degradation of the aptazyme."

However, Scaringe et al teaches the use of 5'-O-silyl-2'-O-orthoester protecting groups that will "minimize" the opportunity to degrade the RNA (see entire document, especially page 11821, last paragraph).

Thus, it would have been obvious to one skilled in the art at the time the invention was made to use the method automated in vitro selection methods of Hesselberth et al and Cox et al with the "modified" nucleotides of Scaringe et al because Scaringe et al states that these protective groups can be used with RNA and will prevent degradation of said RNA and thus would be obvious to use in situations where the degradation of RNA is to be avoided. Furthermore, one of ordinary skill in the art would have been motivated to use the protecting groups of Scaringe et al because Scaringe et al states that these protecting groups would be useful for solid-phase synthesis and purification of said RNA that subsequently is utilized in the screening methods because RNA has to be "provided" (see Scaringe et al, entire document; see especially page 11821, last paragraph).

Contact Information

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

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26. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

27. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
January 23, 2003


PADMASHRI PONNALURI
PRIMARY EXAMINER